EVALUATION OF CTI (CARDIOPROTECTIVE DRUG) IN SUBJECTS OF CORONARY ARTERY DISEASE HYPERTENSION AND DIABETES MELLITUS

THESIS

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1994 **SATYA-NARAYAN**

C E R T I F I C A T E

This is to certify that the work entitled "EVALUATION OF CTI(CARDIOPROTECTIVE DRUG) IN SUBJECTS OF CORONARY ARTERY DISEASE, HYPERTENSION AND DIABETES MELLITUS," which is being submitted as a thesis for M.D. (Medicine) Examination, 1994 of Bundelkhand University, has been carried out by Dr. Satya Narayan in the department of Medicine, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the department as per university regulations.

Dated: Sept., 1993.

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Dated : Sept., 1995.

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A C K N O W L E D G E M E N T S

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Dated: Sept., 1993.

Satya Narayan

(Satya Narayan)

C O N T E N T S

I N T R O D U C T I O N

INTRODUCTION

Ischaemic heart disease consists of major cause of mortality in present stress age and is a global problem involving both developing as well as developed countries (W.H.O., 1982; Hiroyasu et al, 1989; Gordon, 1977). Main risk factors of ischaemic heart disease are atherosclerosis and hyperlipidemia leading to deposition of lipids on the intima of arteries causing narrowing of vessels. Due to narrowing of vessels, specially coronary arteries, blood supply to heart becomes deficient resulting into myocardial ischaemia (Edwin, 1990; Lewis, 1988).

Relation of serum level of total cholesterol to coronary heart disease (or atherosclerotic heart disease) is well established (WHO, 1982; Atherosclerosis study group, 1984; Stamler, 1986; Conference on health effects of blood lipids, 1979).

An increased risk of coronary heart disease (CHD) is associated with a high serum total cholesterol concentration (Gordon, 1977; Neaton, 1984; Goldbourt, 1985; Grundy, 1986; 1987; Thomas, 1990) and low density lipoprotein (LDL) cholesterol (Kannel et al, 1971; Keys et al, 1972; Brown et al, 1986; Steinberg et al, 1989), a low high density lipoprotein (HDL) (Kannel et al, 1979; Goldbourt, 1985; Castelli, 1986a) and in some circumstances high triglycerides (Castelli, 1986b).

Increased lipids :triglycerides, total cholesterol, LDL and very low density lipoprotein(VLDL) cholesterol and decreased HDL cholesterol are the major factors in causing atherosclerosis and ischaemic heart disease (IHD) (Bhatia, 1980).

The analysis of results of serum cholesterol levels and six year mortality from stroke in 350,977 men screened for the multiple risk factors intervention trial (MRFIT) showed that the rate of mortality due to coronary heart disease was 124.4 and 160.3 per 10,000 among the men aged 35-57 years with S. cholesterol levels more than 280 and 300 mg/dl respectively. This rate was highest in the study. It was also observed that within every cholesterol category age adjusted death rates from coronary heart disease were higher than for all strokes. Death rate from CHD and that from all cardiovascular diseases were positively associated with serum cholesterol levels (Hiroyasu et al, 1989).

Of particular clinical significance is the evidence that certain plasma lipoprotein abnormalities are casually related to atherosclerosis and atherosclerotic heart disease and others are predictive of a high risk of this disorder(Lewis,1988). Elevation of serum cholesterol level or more specifically a low density lipoprotein(LDL) cholesterol level is widely accepted as a major risk factor for development of ischaemic heart disease (Key, 1972; Kannel et al, 1971).

Recent clinical and experimental studies of various kinds have firmly established that elevated plasma concentrations of LDL are associated with accelerated atherogenesis (Tyroler, 1987; Goldstein et al, 1977; Steinberg; 1983; 1989).

There is now good evidence from clinical trials and other observations that reduction of serum cholesterol in men with high concentrations can reduce the incidence of coronary heart disease (Consensus conference, 1985; Committee on medical aspects, 1984; Lipid Research Clinic, 1984a, 1984b). Clinical trials in selected patients seem to indicate that effective modification of risk factors (e.g. plasma lipid level) can slow the growth of coronary atherosclerosis (Edwin, 1990). Clinical intervention studies have demonstrated the therapeutic value of correcting hypercholesterolemia (Tyroler, 1987; Lowering blood cholesterol, 1985).

Medical scientists are of the opinion that anti-lipidemic, antidiabetic and antihypertensive drugs and other measures that can decrease catecholamine levels are considered to be remedy for myocardial infarction (Raab, 1971). It is now a well established fact that reduction in blood cholesterol levels reduces the risk of myocardial ischaemia. 25% reduction of blood cholesterol levels reduces the risk of myocardial ischaemia by 50% (Lowering blood cholesterol 1985; Tyroler, 1987).

Vigorous global research is going on to search the agents to control hyperlipidemia. Indian scientists have directed their research towards herbs having hypolipidemic and cardioprotective potential based on few references in age old Ayurvedic texts.

The present formulation is based upon the thorough research data accumulated so far (Satyavati et al, 1966; 1969a; 1969b; 1987; Sastry, 1967; Saxena, 1980; Tripathi et al, 1968; 1975; 1976; 1979; 1984; Dwivedi et al, 1987; 1988; 1989). Hence it was felt desirable to conduct clinical trials on this new combination of age old hypolipidemic/cardioprotective herbal drugs, Terminalia arjuna W & A bark, Inula racemosa hook root and Commiphora mukul ex stocks resin with the primary aim of analyzing the effect of the drug on different components of serum lipids i.e. on total serum cholesterol, triglycerides, VLDL, LDL and HDL in hypertension, diabetes mellitus and coronary artery disease.

REVIEW OF LITERATURE

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Ischemic heart disease consists of major cause of mortality in present stress age and is a global problem, involving both developing as well as developed countries (Gordon, 1977; WHO, 1982; Hiroyasu et al, 1989). Main risk factors of ischemic heart disease are atherosclerosis and hyperlipidemia leading to deposition of lipids on the intima of arteries causing narrowing of vessels. Due to narrowing of vessels, specially coronary arteries, blood supply to heart becomes deficient resulting into myocardial ischaemia (Lewis, 1988; Edwin, 1990).

A number of conditions and habits present more frequently in individuals who develop atherosclerosis than in the general populations, these factors have been termed risk factors. The majority of people below age of 65 years afflicted with atherosclerosis have one or more identifiable risk factors other than aging per se. These are as follows :

1. Male sex.
2. Family history of premature IHD(before age 55 in a parent or siblings).
3. Hyperlipidemia.
4. Cigarett smoking(currently smoking 7/10 cigarettes/day)
5. Hypertension.
6. Low HDL cholesterol (below 0.9 m mol/l. 35 mg/dl)

7. Diabetes mellitus.
8. Personal history of cerebrovascular disease or occlusive peripheral vascular disease.
9. Severe obesity (730% over weight).
10. High lipoprotein (a).

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Increased lipids triglycerides, total cholesterol LDL and very low density lipoprotein (VLDL) cholesterol and decreased HDL cholesterol are the major factors in causing atherosclerosis and ischemic heart disease (IHD) (Bhatia, 1980).

SEQUELAE OF HYPERLIPIDEMIA

Abnormalities of plasma lipid transport are associated with a wide clinical spectrum from silent oberrations of plasma lipoprotein concentration of grave disorders including life limiting cardiovascular, abdominal or neurological manifestation. Of particular clinical significance is the evidence that certain plasma lipoprotein abnormalities are casually related to atherosclerotic/ ischaemic heart disease and other are predictive of a high risk of this disorder (Kannel et al, 1979; Lewis, 1988). Elevated plasma lipoproteins are important clinically because they can cause two life threatening diseases, atherosclerosis and pancreatitis (Brown et al, 1987). Atherosclerosis had dual sequelae as thrombosis and infarction (Brown et al, 1990).

There is striking analogy between serum cholesterol and blood pressure on the epidemiological basis for identifying a large segment of population (10-15%) for intensive treatment (Martin et al, 1986).

The earlier attempts to investigate the biochemical nature of the atherosclerotic lesion incriminated cholesterol (Vogel, 1847; Windaus, 1910). Modern investigations continue to show cholesterol particularly cholesterol esters, as the principal lipid ingredient of the atherosclerotic lesion (Bottcher et al, 1960; Smith, 1965; Insull et al, 1966). From the very beginning animal experiments designed to produce the induction of hypercholesterolemia by one or the other means (Wacher et al, 1913;

Anitschkow et al, 1933; Strong, 1976 and Gresham, 1976).

Epidemiologic studies of the evolution of cardiovascular disease in human populations have for many years emphasized the importance of serum total cholesterol as a precursor of coronary heart disease (Rosenmann et al, 1967; Keys, 1970; Kannel et al, 1971; Carlson et al, 1972; Westlund et al, 1972; Wilhelmsen et al, 1973; Gordon et al, 1974 and McGee et al, 1976). As a result of the great amount of researches conducted into the transport and intermediary metabolism of blood lipids during the past two decades attention has been focussed on the partition of the serum total cholesterol in the various lipoprotein fractions (Gofman et al, 1966 and Frederickson et al, 1967) and the atherogenic potential of each of the latter.

Epidemiological studies initially focussed almost exclusively on the serum total cholesterol showing a powerful relation of this lipid to the subsequent development of coronary heart disease (Stewart et al, 1955; Doyle et al, 1957; Chapman et al, 1957; Keys et al, 1958; Stamler et al, 1960; Paul et al, 1963 and Keys et al, 1963).

Atherosclerosis, a sequel of hyperlipidemia, is a patchy nodular type of arteriosclerosis. The lesions commonly classified as fatty streaks, fibrous plaques and complicated lesions. They are characterised by an accumulation of lipid-filled smooth muscle cells and macrophages (foam cells) and fibrous tissue in focal areas of the intima.

There is a relation between fatty streaks and fibrous atherosclerotic plaques. In the coronary arteries , the extent of fatty streaks may be better indicator of clinically significant raised lesions later in life. Fibrous plaques, also called raised lesions or pearly plaques, are palpably elevated areas of intimal thickening and represent the most characteristic lesion of advancing atherosclerosis. The plaque is much thicker than the normal intima. Although the lipid, like that of fatty streaks, is mainly cholesterol ester, the principal esterified fatty acid is linoleic rather than oleic. Thus plaque cholesterol ester composition differs from fatty streaks but resembles plasma lipoproteins. The complicated lesion is a calcified plaque containing various degrees of necrosis, thrombosis and ulceration. With increasing necrosis and accumulation of gruel the arterial wall progressively weakens, and rupture of the intima can occur causing aneurysm and haemorrhage. Arterial embolism form when fragments of plaque dislodge into lumen. Stenosis and impaired organ function result from gradual occlusion as plaque thicken and thrombi form (Edwin, 1987).

Although the term generalised atherosclerosis is commonly used clinically, lesions are actually irregularly disturbed: different vessels are involved at different ages and to varying degrees (Edwin, 1987).

In the coronary arteries, raised lesions are most prominent in the main stem, the highest incidence being a

short distance beyond the ostia.

Atherosclerosis is nearly always found in the epicardial (extramural) portions of the vessel, while the intramural coronary arteries are spared. Coronary atherosclerosis is often diffused (Edwin, 1987).

Atherosclerotic plaques vary in composition. Their major components include smooth muscle cells, cholesteryl esters and other lipids, collagen and glycosaminoglycans. In patients dying of myocardial infarction and in most instances of sudden cardiac arrest the great majority have severe extensive coronary atherosclerosis. Superadded coronary thrombosis is usually present in the vessel supplying the site of full thickness myocardial infarction; and increasing evidence indicates a role of localised coronary spasm in precipitating at least some acute occlusions (Lewis, 1988).

The analysis of results of serum cholesterol levels and six year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial(MRFIT) showed that the rate of mortality due to coronary heart disease was 124.4 and 160.3 per 10,000 among the men aged 35-57 years with serum cholesterol levels more than 280 and 300 mg/dl respectively. This rate was highest in the study. It was also observed that within every cholesterol category age adjusted death rates from coronary heart diseases were higher than for all strokes. Death rate from CHD and that from all cardiovascular diseases were positively associated

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There is now good evidence from clinical trials and other observations that reduction of serum cholesterol in men with high concentrations can reduce the incidence of coronary heart disease (Consensus conference, 1985; Committee on medical aspects, 1984; Lipid Research Clinic, 1984a; 1984b). Clinical trials in selected patients seem to indicate that effective modification of risk factors(plasma lipid level) can slow the growth of coronary atherosclerosis (Edwin, 1990). Clinical intervention studies have demonstrated the therapeutic value of correcting hypercholesterolemia (Lowering blood cholesterol, 1985; Tyroler, 1987).

Medical scientists are of the opinion that antilipidemic, antidiabetic and antihypertensive drugs and other

measures that can decrease catecholamine levels are considered to be remedy for myocardial infarction (Raab, 1971). It is now a well established fact that reduction in blood cholesterol levels reduces the risk of myocardial ischemia. Twenty five percent reduction of blood cholesterol levels reduces the risk of myocardial ischaemia by 50% (lowering blood cholesterol, 1985; Tyroler, 1987).

HYPERTENSION

High blood pressure is an important risk factor for atherosclerosis, mainly ischemic heart disease and cerebrovascular disease. The risk increases progressively with increasing blood pressure, in the Framingham study, ischemic heart disease incidence in middle aged men with blood pressure exceeding 160/95 was more than five times that in normotensive men (blood pressure 140/90 or less). Hypertensive men and women are both affected, with the diastolic pressure perhaps being more important. In industrialized populations, blood pressure appears to increase inexorably with age, however, the nature of this age relation varies among populations, since there are remote primitive populations that age without any changes in blood pressure levels. The age associated blood pressure increase might be related to physical activity or dietary factors, particularly sodium and total caloric content. In contrast to the other age related risk factors, hypertension appears to increase atherosclerosis throughout the age span.

Conversely, the risk for atherosclerosis appears diminished by therapeutic reduction of blood pressure. Recent intervention studies have shown convincingly that reduction of diastolic levels that had been greater than 105 mm Hg significantly reduces the incidence of strokes, IHD and congestive heart failure in men. Even when patients with diastolic pressure between 90 and 105 mm Hg are similarly maintained on adequate treatment, the incidence of some of these complications may be reduced. Special urgency for relief of hypertension obtains when hyperlipidemia, diabetes or other risk factors are present.

HYPERGLYCEMIA AND DIABETES MELLITUS

Studies in a variety of populations have shown an association of hyperglycemia with clinically evident atherosclerotic disease, suggesting a role of hyperglycemia in atherogenesis. In known diabetics, both insulin dependent and non-insulin-dependent types, there is at least a two fold increase in incidence of myocardial infarction compared with non diabetics. This risk is markedly increased in younger diabetics, and diabetic women are even more prone to ischemic heart disease than are diabetic men. There is an increased tendency toward cerebral thrombosis and infarction but not toward cerebral hemorrhage in diabetes. Gangrene of the lower extremities has been variously estimated to be from 8 to 150 times as frequent in diabetics as in non diabetics and is most often found in diabetics who smoke. Diabetes mellitus is associated with an increase in atherosclerosis observed at autopsy in a variety of populations worldwide, whether the prevalence of atherosclerosis

in a particular population is high or low. The approximately two fold increase in the frequency of hypertension among diabetics, particularly adult females, may accentuate the risk. This relationship is presumably associated with abdominal obesity.

The risk for atherosclerotic disease, however, does not appear to be grossly related to the degree of hyperglycemia among diabetics. Results in the University Group Diabetes Program Study have suggested that reduction of blood glucose by insulin does not appear to influence mortality from established atherosclerosis during a 5 year period. Thus, hyperglycemia and atherosclerosis are associated since there is an increased prevalence of large vessel disease in known diabetics and conversely an increased prevalence of hyperglycemia in association with atherosclerotic disease. These associations remain unexplained and reversibility undocumented. Clinical and experimental studies also support a role for high circulating insulin levels in ischemic heart disease. The capillary microangiopathy, pathognomonic of diabetes mellitus and causing important dysfunction of the kidneys and retina has unknown clinical significance in relation to atherosclerotic disease in larger arteries.

Vigorous global research is going on to search the agents to control hyperlipidemia, hypertension and diabetes mellitus. Indian scientists have directed their research towards herbs having hypolipidemic/antihypertensive/

antidiabetic and cardioprotective potential based on few references in age old Ayurvedic texts.

The present formulation is based upon the thorough research data accumulated so far (Satyavati, et al, 1966; 1969a; 1969b; 1987; Sastry, 1967; Tripathi et al, 1968; 1975; 1976; 1979; 1984; Saxena, 1980; Dwivedi et al, 1987; 1988 and 1989).

THE PRESENT DRUG COMBINATION

Each capsule contains :

Terminalia arjuna W & A bark(extract of)	500 mg
Inula racemosa Hook Root (extract of)	500 mg
Commiphora mukul Hook ex stock resin	500 mg

MODES OF ACTION

Though exact mode of action of T arjuna, I. racemosa and gum resin of C. mukul are not known, yet on the basis of above mentioned facts and the researches conducted so far on these plants, few hypotheses regarding the mode of action of each of them, may be offered.

Terminalia arjuna

It increases the levels of HDL cholesterol, which has protective role against atherogenesis (Tiwari et al,1990).

PGE_2 is known to induce coronary vasodilation and hypotension. It also inhibits platelet aggregation. T arjuna enhances PGE_2 like activity thus it might help in preventing myocardial ischaemia (Dwivedi et al, 1987;1988).

It causes significant decrease in circulating catecholamine levels, while in adrenal glands its concentration goes up, thus, it might be acting by inhibiting the catecholamine relaase from adrenal glands into circulation, thus protecting the heart from catecholamine toxicity (Pathak et al, 1987).

It possesses antihypertensive and antiarrhythmic activity, delays myocardial ischaemia in pre-treated animals (Dwivedi et al, 1988).

It has negative ionotropic and negative chronotropic action on isolated spontaneously beating rat atrium (Srivastava et al, 1989).

It increases cardiac output and accentuates auricular and ventricular contraction (Gupta et al, 1976).

It reduces total cholesterol and triglycerides in blood and increases HDL cholesterol (Tiwari et al, 1990; Pathak et al, 1990).

Anti thrombotic, antiarrhythmic and anti-hypertensive action (Pathak et al, 1987).

All these activities, particularly hypolipidemic, enhancement of PGE_2 like activity, negative ionotropic and chronotropic, antiarrhythmic, antihypertensive and HDL cholesterol raising properties contribute to its cardioprotective action.

<u>Inula racemosa Hook</u>

- Significant enhancement of PGE_2 like activity and thus preventing platelet aggregation(Dwivedi et al, 1987).

- Negative ionotropic and negative chronotropic activity on normal as well as atropinized forg's heart (Sharma et al, 1988).
- Potent hypolipidemic and cardioprotective activity (Dwivedi et al, 1988).
- Lowering of diastolic blood pressure, anginal episodes, lowering catecholamine and cortisol levels (Dwivedi et al, 1989).
- Antianginal property (Tripathi et al, 1984a).

Thus hypolipidemic, hypoglycaemic, hypotensive, lipid lowering and catecholamine and cortisol lowering properties, besides significant enhancement of PGE_2 like activity thus preventing platelet aggregation may constitute its mode of action.

Gum resin of C. mukul Hook ex stocks

- Fraction A of gum guggulu reduced the serum cholesterol levels and the pool size by :
  - i) a significant increase in the rate of removal extraction of cholesterol from the body.
  - ii) Causing mobilization of cholesterol from the tissue (as evident clinically by the resolution of xanthomas).
  - iii) decrease in input/synthesis of cholesterol (Malhotra et al, 1973; 1974).
- Increases the rate of degradation of cholesterol by activating the thyroid gland (Tripathi et al, 1975).

- Since crude drug contains ion exchange resins, it is capable of combining with the bile acids and thereby trapping it out of intrahepatic circulation(Satyavati, 1966).

All of the above factors constitute the mode of action of gum resin of C. mukul regarding its potent hypolipidemic action.

CLINICAL STUDIES

1. C. mukul

Guggulu (Gum resin of C. mukul) has been used in medicine since times immemorial. It has been highly praised for its medicinal value in Atharvaveda, which is supposed to be the source of Ayurveda (Atharvaveda Kand 19 Sutra 38). Charak has enlisted it with the class of drugs useful for regaining consciousness (Sangyasthapan) while Sushruta and Vagbhatta have included it in Eladigana (Sushruta Sutra 38/24). Charak, Sushruta and Vagbhatt all the three reputed physicians of the past have mentioned that if a person develops complications because of excessive use of sneha (Snehavyapada and medoroga), he should be treated with guggulu.

Taking lead from an obscure Sanskrit Shloka in Sushruta Samhita (Sutrasthanam : 15:32).Satyavati (1966) was the first to study guggulu on various experimental and clinical parameters at Banaras Hindu University. A thorough study by other workers followed for about 20 years and

finally the drug was released in 1987 by Prime Minister of India at CDRI, Lucknow.

Preliminary clinical studies were carried out on 22 patients of hypercholesterolemia with associated obesity, ischemic heart disease, hypertension, diabetes etc. Grude guggulu was administered orally in a dose of 5-12 gm in 3 divided doses for 15 days to 1 month. A fall in total serum cholesterol and serum lipid phosphorus was noted in all the cases treated with guggulu. The body weight also revealed a significant decline in 10 patients of obesity (Satyavati, 1966; Dwarkanath and Satyavati, 1970).

Further, studies in 12 cases of hyperlipidemia (9 associated with obesity, 2 ischemic heart disease and 1 case of cerebral thrombosis) showed that oral administration of 12 g of crude guggulu in 3 divided doses for 1 month effectively lowered the serum turbidity and prolonged coagulation time in all the patients (Tripathi et al, 1968).

Clinical efficacy of fraction A of gum guggulu as hypolipidemic agent was evaluated in comparison to ethyl-p-chlorophenoxy isobutyrate and CIBA-13437-Su. Forty four patients classified according to Frederickson's classification were administered these drugs, the selection of patients for each drug being made at random. Fraction A of gum guggulu was administered in the dose of 1.0 g in two divided doses daily. The duration of treatment varied from 6 to 34 weeks. Statistical analysis revealed that fraction A lowered significantly the serum levels of all the lipid fractures (serum total lipids, triglycerides, cholesterol,

phospholipids and beta lipoprotein). The lowering of triglyderides was found most encouraging in case of gum guggulu in comparison to all the known drugs. The side effects observed were hiccough in one patient, diarrhoea in three patients and restlessness and apprehension in one patient (Malhotra et al, 1971).

Faecal sterol studies in 12 cases of hyperlipoproteinemia indicated that both fraction A of guggulu as well as clofibrate enhanced the faecal excretion of sterols by 59% and 49.3% respectively. This long term study indicated that the hypolipidemic effect of fraction A of guggulu could be attributed to : (A) increase in the rate of removal/excretion of cholesterol via gut (B) decrease in the input/synthesis of cholesterol and (c) mobilization of cholesterol from tissues (Malhotra, 1973).

To ellucidate the effect of fraction A on cholesterol metabolism, kinetic studies with 4-C^{14} cholesterol were carried out separately in two series. In the first the effect of drug was investigated without attaining isotopic equilibrium, whereas in the second, the studies were conducted after attaining isotopic steady state (after studies). From the data of this experimental study in rats it could be interpreted that fraction A enhanced the rate of excretion of cholesterol considerably and also reduced the input/synthesis of cholesterol. The cholesterol pool size also decreases after administration of fraction A . Similarly clofibrate inhibited the rate of input/synthesis of cholesterol and increased its rate of excretion signi-

ficantly. In human studies also fraction A of guggulu reduced the serum cholesterol levels and the pool size by causing (i) significantly increase in the rate of excretion of cholesterol and (ii) mobilization of cholesterol from tissues (as evident by resolution of xanthomas clinically (Malhotra et al, 1974).

The effect of guggulu on body weight was studied by Sidhu and associates (1976). In the study 60 obese patients with hyperlipidemia were administered guggulu in the dose of 4 g/day for 8 weeks. Significant reduction of 2.34 kg in body weight was observed in first 4 weeks after that the weight reduction became insignificant. Skin folds of triceps, subscapsular and calf have shown reduction of general and biceps in particularly.

Guggulu was tried on 25 patients of coronary insufficiency. 12-16 g/day of drug was administered for 12 weeks. Serum cholesterol was found to be reduced by 27.8% and triglycerides by 32.7%. Depression of ST segment and correction in T wave inversion was observed in ECG of all the patients of coronary insufficiency (Upadhyaya et al, 1976).

The effect of the drug was studied on 75 patients of obesity associated with other lipid disorders besides arthritis and diabetes mellitus. The dose given was 6-8 g of guggulu per day for a duration of 12 weeks. Fall in body weight was observed at the rate of 1 kg per month. Reduction in total serum cholesterol was found to be 24.5% and serum turbidity was reduced by 15.88%. At the same

time coagulation time of blood was noticeable increased by 68.8%. This last finding is important in consideration of administration of the drug in the patients of atherosclerotic heart disease (Tripathi et al, 1976).

In a long term clinical study, 41 cases of hyperlipoproteinemia were followed up after therapy for 75 weeks with fraction A of guggulu 1.5 g/day. Ten cases were treated with clofibrate 2.0 g/day for a mean period of 75 weeks. Statistically significant reduction was observed in total cholesterol (36.8%) and triglycerides (50.4%) with fraction A while clofibrate also reduced total cholesterol (43.5%) and triglycerides (50.2%). Guggulu resolved completely xanthomas in three cases while clofibrate resolved in one out of three cases. Neither fraction A nor clofibrate was found to reduce the body weight. Except mild diarrhoea in 5 cases no other side effect were observed with guggulu (Malhotra et al, 1977).

Fraction A of guggulu in the dose of 1.0 g/day was found to reduce the total blood cholesterol by 4.5% (Kuppurajan et al, 1978).

Guggulu given in the dose of 12-16 g/day for 12 weeks to 25 patients of hyperlipidemia with associated disorders was reported to reduce the cholesterol by 35.8% in 96% cases, triglycerides by 32.7% in 88% cases, free fatty acids by 62.12% and serum phospholipids by 40% besides reducing the body weight at the rate of 1.4 kg per month (Gupta et al, 1978).

Guggulipid in the dose of 1.2 g/day for 6 weeks reduced cholesterol by 15% and triglycerides by 20%(Saxena, 1980), while in another study where guggulipid was administered in the dose of 1.5 g/day for 12 weeks it was recorded to bring down the levels of cholesterol by 16.9% and triglycerides by 27.13% (Agarwal et al, 1986).

Upathyaya and co-workers (1982) studied the effect of guggulu powder on a long series of patients. Guggulu powder in the dose of 8 g/day was administered to 135 patients of ischaemic heart disease for a duration of 12 weeks. Complete improvement in precordial pain was noted in 75% of patients, and in dyspnoea on effort in 72% of cases. Reduction in body weight was found to be 1 kg per month. 14% of patients showed complete improvement in ECG changes of ischaemic heart disease. Biochemical investigation in these patients revealed reduction in serum cholesterol(27%), serum triglycerides (36%), phospholipids (20%) and free fatty acids (37%). Its hypolipidemic effect was found to be better than that of clofibrate.

Fraction A of guggulu administered in the dose of 1.5g/day for 12 weeks to 85 patients of hyperlipidemia and allied disorders showed significant reduction in body weight in first four weeks specially in relation to triceps folds. Significant reduction in total serum cholesterol, total lipids and triglycerides levels was also observed (Kotiyal et al, 1984).

A 1 : 1 combination of guggulu and Pushkara moola (I. racemosa) was assessed for its clinical efficacy on the patients of ischaemic heart disease. The drug was dispensed in the dose of 6 g/day for 16 weeks to 50 patients of ischaemic heart diaease. The results showed that 10% cases were cured (no precordial pain, and serum lipids and ECG abnormalities normalised), 60% patients relieved (improvement only in precordial pain), however, no improvement was observed in the remaining 10% of cases. The combination lowered total serum cholesterol level by 17.4% (Tripathi et al, 1984).

Guggulipid in the dose of 1.2 g/day was given to 23 patients of hyperlipidemia with hypertension, IHD diabetes mellitus, diabetes mellitus with hypertension, IHD with hypertension and gout, for a period of 4 weeks. The aim of the study was to evaluate the safety of the drug on long term administration of human beings. The drug was found to be completely safe and did not produce any alteration in hepatic or renal functions blood sugar levels, haematological parameters and electrocardiogram. It significantly lowered the serum cholesterol by 27.4% and triglycerides by 48.7% to 78.9% of patients(Agarwal et al, 1986).

Thus the significant reduction in serum cholesterol triglycerides, phospholipids and free fatty acids, improvement of ECG abnormalities, reduction of weight and no side effects besides the lipid lowering capacity being comparable to presently available drugs, justifies the inclusion of

guggulu in the present formulation.

2. T. arjuna

Vagbhatta (700A.D.) was the first to advocate the use of T arjuna in cardiac ailments. He prescribed the use of bark powder. He did not mention any specific cardiac disorder in which it could be more effective. Later on Chakradatta (1700) advised it for (burning of the chest. He prescribed the powder of the outer coating of the bark diluted with milk for the 'relief of pain caused by heart', a condition similar to that of the present day angina pectoris. In addition he also prescribed its administration with water or ghee. Bhavamishra (1700) a contemporary of Chakradatta also advised the use of bark powder of T arjuna in chest pain due to cardiac ailments.

Its use in congestive heart failure was prompted mainly by cardiotonic property attributed it. However, it did not have any effect on it except for a mild diuretic action (Koman, 1920; Ghosh, 1926, Caius et al, 1938). Colabawalla (1951) found the decoction of T arjuna bark to be more useful in hypertensive heart disease compared to congestive heart failure. This apparently made it clear that the drug might be acting through other mechanism apart from its diuretic action. The initial belief of its cardiotonic property obviously could not be validated in these studies. The attention was then diverted to its utility on ischaemic heart disease. Chaturvedi (1973)

first used alcoholic decoction of bark in stable cases of ischaemic heart disease and found that the prolonged use of this drug brings sense of well being and increases euglobulin lysis time and prothrombin time. He also described electrocardiographic improvement following the use of this drug. Subsequently another report about its utility in complete heart block of ischaemic etiology has been published. This particular patient, an adult male who developed stokes Adam's attacks following chest pain, became well after 3 months use of crude powder of T arjuna (Udupa, 1986). Recently in another study 500 mg crude drug powder of T. arjuna was administered in 30 patients of stable angina pectoris. The drug was useful in elleviating the anginal pain. It was also noted to the useful in the cases of ischaemic heart disease associated with rhythm disturbances, particularly premature beats. The drug was found to be beneficial in modifying various known coronary risk factors like obesity, hypertension, diabetes mellitus, and circulating catecholamines in these patients. No significant side effects were observed by these workers. This study has further corroborated the ancient observation of the usefulness of T. arjuna in cardiac pain. Ambasta (1986) found the drug to be effective in hypertension. Dwivedi (1988) confirmed the efficacy of the drug in reducing intensity and frequency of angina pectoris, improvement in effort tolerance, modification of myocardial ischaemia risk factors and cardioprotective action.

3. I. racemosa

Charak Samhita (Old Ayurvedic text book of medicine) was the first to advocate the administration of I. racemosa root powder to the patients of hiccough, asthma and pain on sides of chest (parshwashoola, angina pectoris). Later Bhavamishra (author of Bhavaprakash Nighantu) also referred to its beneficial effects in anginal pain. Chopra et al (1956) has mentioned it to be used as expectorant and resolvement of indurations. Uniyal (1982) wrote about its efficacy in 'Vatarogas' (disorders characterised by different types of pains and neurological diseases).

Water extract of I. racemosa roots was used in a series of 44 patients and showed improvement in pulmonary functions, haematological picture and general health (Singh et al, 1983).

Probably taking a lead from Charak and Bhavamishra the drug (root powder) was tried in 9 patients of ischaemic heart disease. It showed significant prevention of post exercise S-T segment depression in all the patients of ischaemic heart disease and results were found to be comparable to nitroglyceride (Tripathi et al, 1984a). Further a combination of root powder of I. racemosa and also gum resin of C. mukul (guggulu) in the dose of 6000 mg/day was given to 50 patients of ischaemic heart disease. It completely cured 5 patients, significant improvement in ECG patients was noted in 40 patients and 5 patients failed to respond to drug (Tripathi et al, 1984b).

In a study on a series of 60 patients the water extract of I. racemosa was given in the dose of 1500 mg/day. Significance reduction in number of episodes of angina pectoris, significant improvement in ST depression and T wave inversion in ECG of the patients were important observations, however, it had no significant effect on blood pressure (Dwivedi et al, 1989).

AIMS OF THE STUDY

AIMS OF STUDY

The present study was conducted in 25 patients with hypertension, diabetes mellitus and coronary artery disease in the department of Medicine, M.L.B. Medical College, Jhansi with the following aims :

1. To analyse the effect of a new combination of three herbal drugs on hypertension, diabetes mellitus and coronary artery disease.
2. To analyse its effect on lipid profile.

MATERIAL AND METHODS

MATERIAL AND METHODS

The present study was conducted on 25 subjects from two sources :

1. Those admitted in the medical wards of M.L.B. Medical College, Hospital, Jhansi.
2. Those attending the hypertension clinic, department of medicine, M.L.B. Medical College, Hospital, Jhansi.

Detailed history revealed that 13 subjects were suffering from hypertension while 6 were suffering from combination of coronary artery disease (CAD) and hypertension, 4 were suffering from diabetes mellitus with hypertension and 2 were suffering from combination of hypertension, diabetes mellitus and coronary artery disease.

DESIGN OF TEST

Informed consent was taken from each subject. The subjects were asked to have their normal dinner on the previous night and not to take anything after this except water. Next morning fasting blood sample was taken. Then the subjects were asked to take the drug in a regular dosage of two capsules twice daily for 3 months. Similar monthly blood samples were taken. During the study period they were told not to change their dietary or personal habits as this could otherwise have effect on the lipid

profile.

Serum was separated from the blood samples and following tests were performed :

A. SERUM TOTAL CHOLESTEROL (STC)

It was estimated by following method using chemical kits of Ethnor.

1. Added 5 ml of cholesterol reagent in each of three test tubes name T, S, and B for 'test', Standard' and Blank respectively.
2. To this added 25 ul of serum, cholesterol standard (250 mg/dl) and distilled water in T, S, and B respectively.
3. Mixed them well for 10 seconds and placed in a boiling water bath for exactly 45 seconds.
4. Cooled them immediately in running tap water and mixed their contents.
5. Optical densities were read at 560 nm, setting the blank as zero.
6. Serum cholesterol calculated by the formula :

$$\text{STC (mg/dl)} = \frac{\text{Optical density of test}}{\text{Optical density of standard}} \times 250$$

B. SERUM TRIGLYCERIDES (STG)

It was estimated by using enzymatic kits of Ethnor employing following method :

1. Reconstituted each vial of reagent I (supplied in the form of lyophilised enzymes) in 2.5 ml distilled water.

2. Took 0.5 ml of reconstituted reagent I in each of three test tubes labelled T, S and B for test, Standard and Blank respectively.
3. To this added 0.5 ml of reagent II(Phenol solution) in each of three test tubes labelled T, S and B and mixed them all well.
4. To this added 20 ul of serum triglyceride standard (300 mg/dl) and distilled water in T, S and B respectively, mixed well and incubated at $37^{\circ}C \pm 0.5^{\circ}C$ for 10 minutes.
5. Finally 2 ml of distilled water added to all three tubes, mixed and reading taken at 500 nm setting the blank at zero.
6. Triglyceride calculated by using the formula :

$$\text{STG (mg/dl)} = \frac{\text{Optical density of test}}{\text{Optical density of standard}} \times 300$$

C. ESTIMATION OF HDL CHOLESTEROL

It was also estimated by using the enzymatic kits of Ethnor by following method :

1. To precipitate the LDL and VLDL cholesterol and chylomicrons, mixed 0.5 ml of lipogent reagent with equal amount of serum and kept at room temperature($25 \pm 5^{\circ}C$) for 10 minutes. Then centrifuged it at 2000 rpm for 20 minutes.
2. Working standard was prepared by diluting the provided standard with distilled water in the ratio of 1 : 7.

3. Working reagent was prepared by mixing the reagent I lyophilised enzymes) with reagent II(Phenol solution).
4. Took 1.0 ml of working reagent in each of three test tubes labelled T, S and B for test, Standard and Blank respectively.
5. To this added 100 ul of supernatant (obtained in step I0 working standard and distilled water to T, S and B respectively and mixed them well.
6. After incubating all the tubes at 37°C for 15 minutes added distilled water 4.0 ml to each and reading taken at 515 nm after mixing the tubes well and setting the Blank at zero.
7. HDL cholesterol calculated by the formula :

$$\text{HDL (mg/dl)} = \frac{\text{Optical density of test}}{\text{Optical density of standard}} \times 50$$

D. LDL ESTIMATION

LDL cholesterol was directly calculated by Friedwald's formula :

LDL (mg/dl) = STC - (STG/5 + HDL).

E. ELECTROCARDIOGRAPHY

E.C.G. was recorded monthly and observed ST segment changes.

Simultaneously, routine biochemical tests were done at monthly intervals to check any associated change in these parameters.

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O B S E R V A T I O N S

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OBSERVATIONS

The present study was carried out on 25 subjects with hypertension, diabetes mellitus and coronary artery disease (CAD). They were given the hyperlipidaemic/ cardioprotective drug in regular dosage of two capsules twice a day for 6 months. Basal and monthly blood samples and electrocardiogram were calculated and lipid profile was done. Before analysing the data, the subjects were grouped into four categories :

Group I : Patients having hypertension on the basis of blood pressure above 160/90 mm Hg.

Group II : Patients having hypertension with diabetes mellitus (fasting blood sugar 7120 mg%).

Group III: Patients having hypertension with coronary artery disease.

Group IV : Patients having hypertension with diabetes mellitus and coronary artery disease.

Thus, the data obtained, were analysed for any change in different parameters of lipid profile, fasting blood sugar, blood pressure (systolic/diastolic) and S-T segment in electrocardiogram inducible by the drug in all subjects in different groups. Also the present study recorded the doses of different drugs which the patients were already receiving to see any change in the same.

TABLE I : Showing the distribution of cases according to their age and sex.

Age group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
31 - 40	-	-	5	38.46	5	20.00
41 - 50	1	8.33	2	15.38	3	12.00
51 - 60	5	41.66	3	23.07	8	32.00
61 - 70	3	25.00	2	15.38	5	20.00
71 - 80	3	25.00	1	7.69	4	16.00
TOTAL	12	100.00	13	100.00	25	100.00

Table I shows age and sex distribution of all 25 subjects. Out of 25 patients, 12 cases were males and 13 females constituting a ratio of 1 : 1. Majority (32%) of the patients were in the age group of 51-60 years. Out of 8 cases in this age group, 5 were males and 3 were females.

TABLE II : Showing the distribution of cases according to various diseases.

Diseases	No.of cases	Percentage
Hypertension	12	48.00
Hypertension + C.A.D.	5	20.00
Hypertension + diabetes mellitus	5	20.00
Hypertension + CAD + DM	3	12.00
TOTAL	25	100.00

Table III shows the disease-wise distribution of all cases. All 25 subjects were having hypertension, but 12(48%) of them were not having any other illness whereas 5(20%) cases had coronary artery disease also and another 5(20%) were suffering from diabetes mellitus as well. Only 3(12%) cases were those who had all three diseases i.e. hypertension, diabetes mellitus and coronary artery disease.

TABLE III : Showing serum total cholesterol changes in patients of hypertension (Group I).

Name	Serum total cholesterol (mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
S.R.	308	280	260	292	300	285	263
M.B.	192	190	176	170	170	170	178
G.R.	269	260	230	220	200	198	198
R.K.	182	200	200	190	190	194	194
D.	250	242	230	224	212	200	200
B.D.	250	244	232	225	220	216	212
M.R.	173	170	170	166	154	154	154
U.	211	210	208	190	182	170	160
N.K.	211	200	190	198	198	190	170
BK	231	230	212	206	208	208	216
P.	211	204	200	194	200	186	176
S.K.	308	290	270	256	248	240	235
Mean ±SD	233 ±45	227 ±37	215 ±31	211 ±36	207 ±38	201 ±35	196 ±32

't' test - 0 : 1 month p $<$0.05
1 : 2 month p $<$0.0005
2 : 3 month p $>$0.05
3 : 4 month p $>$0.05
4 : 5 month p $<$0.005
5 : 6 month p $<$0.05
0 : 6 month p $<$0.0005

Table III shows the STC changes in patients with hypertension. The mean±sd basal serum total cholesterol value was 233±45 mg/dl and it fell to 227±37 mg/dl after one month and the change was statistically significant (p $<$0.05). Again it came down to 215±31 mg/dl after 2 months of treatment and the difference was highly significant (p $<$0.0005) as compared to the values at 1 month. After another 1 month of treatment, it was 211±36 mg/dl but it was not differ from the 2 months STC (p $>$0.05). The mean STC decreased to 207±38 mg/dl after 5 months. The difference statistically highly significant (p $<$0.005) as compared to the values at 4 months. The final values were 196±32 mg/dl. The difference was significant (p $<$0.05) as compared to the values at 5 months. On comparing the basal STC from the 6 month values the change was highly significant statistically (p $<$0.0005).

TABLE IV : Showing serum triglycerides changes in patients of hypertension (Group I).

Name	Serum triglycerides values(mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	months 6
S.R.	223	200	188	188	180	180	76
M.B.	69	64	60	58	58	58	58
G.R.	231	202	186	186	178	178	176
R.K.	107	120	120	126	120	120	110
D	161	166	150	146	144	140	136
B.D.	130	130	128	128	126	122	120
M.R.	84	80	72	70	74	76	76
U.	70	70	66	66	64	64	63
N.K.	177	175	175	170	170	166	160
B.K.	223	210	202	190	192	180	172
P.	160	162	160	138	130	122	120
S.K.	161	170	170	150	150	140	142
Mean ±SD	150 ±59	146 ±52	140 ±50	135 ±48	131 ±45	129 ±44	126 ±43

't' test : 0 : 1 month p $<$0.05 4 : 5 month p $<$0.005
1 : 2 month p $<$0.005 5 : 6 month p $<$0.01
2 : 3 month p $<$0.05 0 : 6 month p $<$0.0025
3 : 4 month p $<$0.005

Table IVshows serum triglyceride changes in patients having only hypertension. The basal STG was 150±59 mg/dl. After one month it decreased to 146±52 mg/dl and change was statistically significant (p $<$0.05). After 2 months of treatment it came down to 140±50 mg/dl and again the change was significant (p $<$0.005). At 3 months, STG was 135±48 mg/dl. It was also significantly different from the 2 months value (p $<$0.05). It further came down to 131±45 mg/dl after another one month of treatment and

and the change was significant ($p < 0.005$). The mean ±SD of 5th month values was 129±44 mg/dl. Again it was statistically different from the 4 month values ($p < 0.005$). The final STG was 126±43 mg/dl which differed from previous value ($p < 0.01$). On comparing the basal STG from the final value the change was highly significant ($p < 0.0025$).

TABLE V : Showing serum HDL cholesterol changes in patients of hypertension (Group I).

Name	Serum HDL Cholesterol (mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
S.R.	37	35	35	37	39	39	41
M.B.	45	45	46	48	48	48	48
G.R.	35	38	40	40	40	42	42
R.K.	42	42	42	40	42	42	43
D	30	36	35	40	40	40	40
B.D.	38	38	38	40	40	41	41
M.R.	36	38	44	45	46	46	46
U.	50	50	52	50	50	50	50
N.K.	30	36	38	35	36	36	37
B.K.	34	38	38	36	38	39	39
P	32	38	44	44	42	42	44
S.K.	30	28	36	38	38	40	41
Mean±SD	37±6	38±5	41±5	41±5	42±4	42±4	43±4

't' test : 0 : 1 month
1 : 2 months
2 : 3 months
3 : 4 months
4 : 5 months
5 : 6 months
0 : 6 months

$p > 0.05$

Table V shows that there was no significant changes in serum HDL cholesterol levels in these patients who had hypertension even after full 6 months of drug treatment ($p > 0.05$). The mean $\pm$SD of HDL values at 0, 1, 2, 3, 4, 5 and 6 months were 37 ± 6, 38 ± 5, 41 ± 5, 42 ± 4, 42 ± 4 and 43 ± 4 mg/dl respectively.

Table VI shows the changes in blood press in patients of hypertension group. The montly mean systolic blood pressure values were 164 ± 23, 161 ± 18, 150 ± 12, 143 ± 8, 141 ± 7, 140 ± 7 and 140 ± 8 mm Hg respectively. On applying 't' test, it was seen that the change was statistically different at each month ($p < 0.05$) except 0-1 and 4-5 months ($p > 0.05$). On comparison the basal value from the final value the change was highly significant ($p < 0.0025$). Similarly the monthly mean diastolic blood pressure values recorded were 106 ± 14, 96 ± 10, 92 ± 9, 89 ± 9, 89 ± 9, 88 ± 10 and 88 ± 10 mm Hg. The monthly changes were statistically different between 0-1, 1-2 and 2-3 months ($p < 0.0025$, < 0.025 and < 0.025 respectively) but insignificant thereafter ($p > 0.05$). The 0-6 months change was highly significant statistically ($p < 0.0005$).

TABLE VI : Showing blood pressure changes (Systolic/diastolic) in patients of hypertension (Group I).

Name	Values of systolic and diastolic blood pressure (mm Hg).													
	0 month		1month		2 months		3 months		4 months		5 months		6 months	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D
S.R.	148	106	140	100	140	100	140	100	138	96	140	100	144	100
M.B.	138	98	160	80	152	80	140	76	140	76	140	74	136	74
G.R.	140	100	140	92	130	80	130	80	132	80	132	80	130	80
R.K.	146	100	150	100	150	100	150	100	146	98	146	98	146	98
D.	180	80	162	76	160	76	136	76	132	74	132	74	130	70
B.D.	160	120	198	110	140	92	140	90	136	94	136	94	138	96
M.R.	186	120	172	100	160	100	148	94	140	90	140	90	136	88
U.	140	98	140	86	134	86	130	86	136	86	130	86	130	86
N.K.	180	100	176	96	170	96	152	88	150	88	146	84	146	84
B.K.	212	136	180	106	160	100	146	98	146	98	150	100	150	100
P.	170	110	154	100	150	90	144	86	144	86	140	82	140	82
S.K.	168	100	160	100	156	98	156	98	152	98	150	96	150	96
Mean ±SD	164 ±23	106 ±14	161 ±18	96 ±10	150 ±12	92 ± 9	143 ± 8	89 ± 9	141 ± 7	89 ± 9	140 ± 7	88 ±10	140 ± 8	88 ±10

't' test :

Systolic BP

0 : 1 month p $>$ 0.05
1 : 2 months p $<$ 0.05
2 : 3 months p $<$ 0.05
3 : 4 months p $<$ 0.05
4 : 5 months p $>$ 0.05
5 : 6 months p $<$ 0.05
0 : 6 months p $<$ 0.0025

Diastolic BP

0 : 1 month p $<$ 0.0025
1 : 2 months p $<$ 0.025
2 : 3 months p $<$ 0.025
3 : 4 months p $>$ 0.05
4 : 5 months p $>$ 0.05
5 : 6 months p $>$ 0.05
0 : 6 months p $<$ 0.0005

TABLE VII : Showing changes in dose of antihypertensive drug in patients of hypertension.

Name	Dose of antihypertensive drug (Atenolol) (mg/day)						
	Month 0	Month 1	Months 2	Months/ 3	Months/ 4	Months 5	Months 6
S.R.	50	50	50	50	50	50	50
M.B.	100	100	100	100	75	75	50
B.R.	100	100	100	100	75	75	75
R.K.	50	50	50	50	50	50	50
D.	100	100	100	100	100	100	100
B.D.	50	50	50	50	25	25	25
M.R.	50	50	50	50	50	50	50
U.	100	100	100	100	50	50	50
N.K.	100	100	100	100	75	75	75
B.K.	50	50	50	50	50	50	50
D.P.	100	100	100	100	100	100	100
S.K.	50	50	50	50	50	50	50
Mean ±S.D.	75 ±26	75 ±26	75 ±26	75 ±26	62 ±23	62 ±23	60 ±22

't' test : 0 : 1 month $p > 0.05$
1 : 2 months $p > 0.05$
2 : 3 months $p > 0.05$
3 : 4 months $p < 0.005$
4 : 5 months $p > 0.05$
5 : 6 months $p > 0.05$
0 : 6 months $p < 0.0125$

Table VII shows changes in the daily requirement of antihypertensive agent atenolol in hypertensive group of patients. The mean initial requirement was 75±26 mg/day and it remained the same upto 3 months.

After 4 months of treatment the requirement came down to 62±23 mg/day and the change was significant ($p < 0.065$). It remained same at 5 months but was reduced to 60±22 mg/day after 6 months of treatment, but this change was statistically insignificant ($p > 0.05$). The 0-6 months requirement change was highly significant ($p < 0.0025$).

TABLE VIII : Showing serum total cholesterol changes in patients of hypertension and CAD.

Name	Serum total cholesterol values (mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.S.G.	308	296	262	246	230	218	210
R.S.	269	260	260	230	220	210	206
R.N.	255	250	240	228	222	210	202
P.L.	182	180	188	190	178	178	175
P.D.	234	210	210	200	200	200	200
Mean ±S.D.	250 ±46	239 ±45	232 ±32	219 ± 23	210 ±21	203 ± 16	199 ±14

't' test : 0 - 1 months $p < 0.05$ 1-2 months $p > 0.05$
2 - 3 months $p < 0.05$ 3-4 months $p < 0.025$
4 - 5 months $p < 0.05$ 5-6 months $p < 0.05$
0 - 6 months $p < 0.025$

Table VIII shows changes in STC in patients of hypertension and CAD. The monthly mean STC values were 250±46, 239±45, 232±32, 219±23, 210±21, 203±16 and 199±14 mg/dl. The monthly change in the STC was statistically significant ($p < 0.05$ for 0-1, 2-3, 4-5 and 5-6; and

p $<$0.025 for 3-4 months) except between one and two months (p $>$0.05). On comparing the basal value from the final STC value it was found that the total change was highly significant (p $<$0.025)(Table VIII)

TABLE IX : Showing serum triglyceride changes in patients of hypertension and CAD.

Name	Serum triglycerides values(mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.S.G.	260	190	172	164	162	160	160
R.S.	200	200	187	176	176	170	170
R.N.	164	160	156	154	150	150	138
P.L.	92	90	90	86	84	84	80
P.D.	175	136	140	152	152	150	144
Mean ±SD	178 ±61	155 ±44	149 ±39	146 ±35	145 ±36	143 ±34	138 ±35

't' test : 0 - 1 month, 1 - 2 months, 2 - 3 months, 3 - 4 months, 4---5 months, 5 - 6 months | p $>$0.05 | 0 - 6 months p$<$0.05

Table IX shows changes in STG in patients having hypertension and CAD. The initial STG was 178±61 mg/dl and fell to 138±35 mg/dl after 6 months of treatment. This change was statistically significant (p $<$0.05). The STG values in the intervening months were 155±44, 149±39, 146±35, 145±36 and 143±34 mg/dl. On applying 't' test, the monthly change in STG was statistically insignificant (p $>$ 0.05).

TABLE X : Showing serum HDL cholesterol changes in patients of hypertension and CAD.

Name	Serum HDL cholesterol values(mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.S.G.	30	30	30	35	38	40	40
R.S.	36	40	44	45	44	45	45
R.N.	40	44	42	48	47	47	46
P.L.	32	36	40	44	44	44	43
P.D.	32	36	40	44	44	44	43
Mean±SD	34±4	36±6	38±6	42±5	42±4	43±3	43±3

't' test : 0 - 1 month, 1 - 2 months, 2 - 3 months, 3 - 4 months, 4 -5 months, 5 - 6 months, 6 - 6 months | p $\nearrow$0.05

Table X shows changes in serum HDL in patients of hypertension and CAD. The monthly mean HDL values were 34±4, 36±6, 38±6, 42±5, 42±4, 43±3 and 43±3 mg/dl respectively. Though there was apparent increase in HDL but it was statistically insignificant at any stage (p $\nearrow$0.05 even between 0-6 months).

Table XI shows monthly changes in Blood pressure in cases of hypertension and CAD. The monthly mean systolic BP values were 148±10, 150±12, 148±4, 137±19, 135±18, 135±19, and 134±17 mm Hg respectively. Though there is no significant monthly change in systolic BP. (p $\nearrow$0.05) but the final value differs significantly from the initial value (p $\swarrow$0.05). Similarly the monthly mean

TABLE XI : Showing systolic and diastolic blood pressure changes in patients of hypertension with CAD.

Name	Values of systolic and diastolic blood pressure (mm Hg)													
	0 month		1 month		2 months		3 months		4 months		5 months		6 months	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D
R.S.G.	150	96	146	90	140	90	136	86	136	86	136	84	130	84
R.S.	160	96	166	90	166	98	160	98	156	98	158	100	156	98
RN.	156	80	158	82	160	80	150	80	144	80	142	80	140	80
P.L.	140	96	146	96	140	90	110	90	106	90	106	76	108	76
P.D.	136	98	136	98	136	98	130	98	132	98	132	98	136	98
Mean ± S.D	148±10	93±7	150±12	91±6	148±14	91±7	137±19	90±8	155±18	90±8	135±19	88±11	134±17	87±10

't' test :

	Systolic BP	Diastolic BP
0 : 1 month	p 70.05	p 70.05
1 : 2 months	p 70.05	p 70.05
2 : 3 months	p 70.05	p 70.05
3 : 4 months	p 70.05	p 70.05
4 : 5 months	p 70.05	p 70.05
5 : 6 months	p 70.05	p 70.05
0 : 6 months	p 70.05	p 70.05

diastolic BP values were 93±7, 91±6, 91±7, 90±8, 90±8, 88±11 and 87±10 mm Hg and there was no significant difference between any two values ($p > 0.05$ even between 0-6 months).

TABLE XII : Showing changes in dose of antihypertensive drug(Atenolol) in patients of hypertension with CAD.

Name	Dose of antihypertensive drug (mg/day)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.S.G.	50	50	50	50	50	50	50
R.S.	100	100	100	100	100	100	100
R.N.	50	50	50	50	50	50	50
P.L.	100	100	100	100	75	75	75
P.D.	50	50	50	50	50	50	50
Mean ±S.D.	70 ±27	70 ±27	70 ±27	70 ±27	65 ±22	65 ±22	65 ±22

't' test :		
	0 - 1 month	p > 0.05
	1 - 2 months	
	2 - 3 months	
	3 - 4 months	
	4 - 5 months	
	5 - 6 months	
	0 - 6 months	

Table XII shows change in the requirement of Atenolol in patients of hypertension and CAD. The mean requirement of the drug remained 70±27 mg/day for three months after which it reduced to 65±22 for remaining 3 months. There was no significant change in the drug dosage ($p > 0.05$).

.LE XIII : Showing ECG changes in patients of hypertension and CAD.

Name	S-T segment depression (mm)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.S.G.	1.5	1.5	1.5	1.5	1.5	1.5	1.5
R.S.	-	-	- -	-	-	-	-
R.N.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
P.L.	1.0	1.0	1.0	1.0	1.0	1.0	1.0
P.D.	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mean ±S.D.	0.8 ±0.6	0.8 ±0.6	0.8 ±0.6	0.8 ±0.6	0.8 ±0.6	0.8 ±0.6	0.8 ±0.6

0 - 6 month change = 0

Table XIII shows ST segment depression in ECGs of patients with hypertension and CAD. It is clear that initially the mean ST segment depression was 0.8±0.6 mm and it remained same throughout the period of study (No change).

TABLE XIV : Showing changes in dose of antianginal drug in patients of hypertension and CAD.

Name	Dose of antianginal drug (Sorbitrate) (mg/day)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.S.G.	15	15	15	15	15	15	15
R.S.	30	30	30	30	30	30	30
R.N.	30	30	30	30	30	30	30
P.L.	20	20	20	20	20	20	20
P.D.	30	30	30	30	30	30	30
Mean±SD	25±7	25±7	25±7	25±7	25±7	25±7	25±7

0 to 6 months change = 0

Table XIV shows the daily requirement of antianginal drug sorbitrate in mg/day. It is clear from the table that the initial requirement was 25±7 mg/day and it remained the same throughout the study.

TABLE XV : Showing serum total cholesterol changes in patients of hypertension with diabetes mellitus.

Name	Serum total cholesterol values (mg/dl).						
	Month 0	Month 1	Months 2	months 3	Months 4	Months 5	Months 6
R.C.	205	205	200	200	200	190	180
R.D.	192	190	198	198	170	170	168
S.	260	260	252	235	220	200	189
PNS	173	170	170	170	162	160	152
R.K.A.	202	200	192	190	190	180	182
Mean ±S.D.	206 ±32	205 ±34	202 ±30	199 ±24	188 ±23	180 ±16	174 ±14

't' test : 0 - 1 month | p 4-5 months p $\angle$0.05
1 -2 months | 5-6 months p $\angle$0.05
2 - 3 months | p$\nsim$0.05 0-6 months p $\angle$0.025
3- 4 months |

Table XV shows STC changes in patients of hypertension with diabetes mellitus. The mean monthly STC values were 206±32, 205±34, 202±30, 199±24, 188±23, 180±16 and 174±14 mg/dl. On applying 't' test it was observed that there was no significant monthly change till 4 months (p $\nsim$0.05), but thereafter it became statistically significant (p $\angle$0.05). On comparing the initial value from the final value, the total change was highly significant statistically (p $\angle$0.025).

TABLE XVI : Showing serum triglyceride changes in patients of hypertension with diabetes mellitus.

Name	Values of serum triglyceride (mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.C.	177	170	160	155	152	152	150
R.D.	155	155	155	150	142	138	138
S.	192	180	156	140	132	124	120
P.N.S.	84	80	72	70	70	68	66
R.K.A.	146	140	130	150	150	152	150
Mean ±SD	151 ±42	145 ±39	135 ±37	133 ±36	129 ±34	127 ±35	125 ±35

't' test :		
	0 - 1 month	p > 0.05
	1 - 2 months	
	2 - 3 months	
	3 - 4 months	
	4 - 5 months	
	5 - 6 months	
	0 - 6 months	

Table XVI shows STG changes in patients with hypertension and diabetes mellitus. The mean monthly STG values were 151±42, 145±39, 139±37, 133±36, 129±34, 127±35 and 125±35 mg/dl. Though there was apparent fall in the STG , but it is statistically insignificant ($p > 0.05$ even between 0 and 6 months).

Table XVII shows serum HDL changes in patients of hypertension and diabetes mellitus. The mean monthly serum HDL values were 35±7, 38±5, 42±5, 44±6, 44±5, 44±5 and 45±5 mg/dl respectively. But no two values were statistically significant ($p > 0.05$ even between 0 and 6 months).

TABLE XVII : Showing serum HDL cholesterol changes in patients of hypertension with diabetes mellitus.

Name	Values of serum HDL cholesterol (mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.C.	45	45	48	50	50	50	52
R.D.	28	35	35	35	36	36	37
S.	30	32	38	46	46	45	45
P.N.S.	36	38	44	45	45	43	43
R.K.A.	38	40	44	46	45	46	46
Mean±SD	35±7	38±5	42±5	44±6	44±5	44±5	45±5

't' test : 0 - 1 month
1 - 2 months
2 - 3 months
3 - 4 months
4 - 5 months
5 - 6 months
0 - 6 months
/ p 70.05

TABLE XVIII : Showing blood sugar (fasting) changes in patients of hypertension with diabetes mellitus.

Name	Values of blood sugar(fasting) (mg%)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.C.	200	178	178	160	160	150	146
R.D.	132	111	110	104	104	104	104
S.	176	199	160	150	150	142	126
P.N.S.	180	188	186	180	186	186	186
R.K.A.	188	116	108	106	108	110	110
Mean ±SD	175 ±26	158 ±42	148 ±37	140 ±34	142 ±35	138 ±33	134 ±33

't' test = 0 - 1 month p 70.05
1 - 2 months p 70.05
2 - 3 months p<0.025
3 - 4 months p 70.05
4 - 5 months p 70.05
5 - 6 months p 70.05
0 - 6 months p<0.025

Table XVIII shows changes in fasting blood sugar in patients with hypertension and diabetes mellitus. The mean monthly fasting blood sugar values were 175±26, 158±42, 148±37, 140±34, 142±35, 138±33 and 134±33 mg/dl. There was no statistically significant change at monthly intervals ($p > 0.05$) except between 2-3 months ($p < 0.025$). On comparing the initial and final values, the change was statistically significant ($p < 0.025$).

TABLE XIX : Showing changes in dose of antidiabetics in patients of hypertension with diabetes mellitus.

Name	Dose of antidiabetics (Glibendamide) (mg/day)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.C.	10	10	10	10	10	10	10
R.D.	10	10	10	10	7.5	7.5	5
S.	15	15	15	15	15	15	15
P.N.S.	10	10	10	10	10	10	10
R.K.A.	15	15	15	10	10	7.5	7.5
Mean±SD	12±3	12±3	12±3	11±1	10±2	10±2	10±3

't' test : 0 - 1 month, 1 - 2 months, 2 - 3 months, 3 - 4 months, 4 - 5 months, 5 - 6 months, 0 - 6 months | $p > 0.05$

Table XIX shows the changes in the requirement of antidiabetic drug glibendamide in patients of hypertension and diabetes mellitus. The mean requirement

of the drug was 12±3 mg/day initially and it remained the same for 3 months, after which it reduced to 11±1 mg/day . After another one month the requirement came down to 10±2 mg/day and thereafter it remained constant. No two values are significantly different ($p > 0.05$ even between 0 and 6 months).

Table XX shows changes in blood pressure in patients of hypertension and diabetes mellitus. The monthly systolic blood pressure were 168±19, 164±15, 150±10, 145±10, 144±8, 141±8 and 141±8 mm Hg. The change was significant only at 2-3 and 3-4 months ($p < 0.0125$ and < 0.05 respectively). On comparing the 0 and 6 month values, it was also significant ($p < 0.05$).

Similarly the mean monthly diastolic blood pressure values were 108±10, 100±4, 97±3, 92±8, 91±9, 91±9 and 87±9 mm Hg. The change was statistically significant only at 0-1, 1-2 and 0-6 months ($p < 0.05$, < 0.05, and < 0.01 respectively).

TABLE XX : Showing changes in systolic and diastolic blood pressure in patients of hypertension with diabetes mellitus.

Name	Values of systolic and diastolic blood pressure (mm Hg)													
	0 month		1 month		2 months		3 months		4 months		5 months		6 months	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D
R.C.	170	110	170	100	160	96	150	90	150	90	148	90	148	90
R.D.	140	98	138	98	140	98	136	78	136	76	136	76	136	76
S.	190	124	174	106	144	100	138	96	138	96	132	94	130	90
P.N.S.	180	110	170	98	146	98	142	98	142	98	140	98	140	82
R.K.A.	160	100	160	98	162	94	160	98	156	96	150	96	150	96
Mean ±SD	168 ±19	108 ±10	164 ±15	100 ± 4	150 ±10	97 ± 3	145 ±10	92 ± 8	144 ± 8	91 ± 9	141 ± 8	91 ± 9	141 ± 8	87 ± 8

't' test	Systolic BP	Diastolic BP
0 : 1 month	p $>$ 0.05	p $<$ 0.05
1 : 2 months	p $>$ 0.05	p $<$ 0.05
2 : 3 months	p $<$ 0.0125	p $>$ 0.05
3 : 4 months	p $<$ 0.05	p $>$ 0.05
4 : 5 months	p $>$ 0.05	p $>$ 0.05
5 : 6 months	p $>$ 0.05	p $>$ 0.05
0 : 6 months	p $<$ 0.05	p $<$ 0.01

TABLE XXI : Showing changes in dose of antihypertensive drug (Atenolol) in patients of hypertension and diabetes mellitus.

Name	Dose of antihypertensive Drug (Atenolol) (mg/day)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.C.	100	100	100	100	75	75	50
R.D.	50	50	50	50	50	50	50
S.	50	50	50	50	50	50	50
P.N.S.	100	100	100	100	100	75	75
R.K.A.	50	50	50	50	50	50	50
Mean ±S.D.	70 ±27	70 ±27	70 ±27	70 ±27	65 ±22	60 ±14	55 ±11

't' test : 0 - 1 month
1 - 2 months
2 - 3 months
3 - 4 months
4 - 5 months
5 - 6 months
6 - 6 months

p $\gtrless$ 0.05

Table XXI shows changes in the requirement of atenolol in patients of hypertension with diabetes mellitus. The mean requirement which was 70±27 mg/day initially remained same for 4 months. The requirement of the drug for next months were 65±22, 60±14 and 55±11 mg/day in the month 4th, 5th and 6th, respectively. No two values differ significantly (p $\gtrless$ 0.05) even between 0 and 6 months.

Table XXII shows STC changes in patients of hypertension with CAD and DM. The monthly mean STC values were 223±26, 215±24, 209±24, 211±34, 203±28, 195±30 and 190±27 mg/dl. The monthly changes were not

statistically significant ($p > 0.05$). But 0-6 months change was significant ($p < 0.05$).

TABLE XXII : Showing serum total cholesterol changes in patients of hypertension with diabetes mellitus and CAD.

Name	Values of serum total cholesterol(mg/dl)						
	Month 0	Month 1	Months 2	Months/Months 3	Months 4	Months 5	Months 6
W.K.	220	208	200	192	190	188	182
A.B.	198	196	190	190	184	170	167
S.P.	250	242	236	250	236	228	220
Mean ±S.D.	223 ±26	215 ±24	209 ±24	211 ±34	203 ±28	195 ±30	190 ±27

't' test : 0-1 month, 1-2 months, 2-3 months, 3-4 months, 4-5 months, 5-6 months — $p > 0.05$

0-6 months $p < 0.005$

TABLE XXIII : Showing serum triglyceride changes in patients of hypertension with diabetes mellitus and CAD.

Name	Values of serum triglyceride(mg/dl)						
	Month 0	Month 1	Months/Months 2	Months 3	Months 4	Months 5	Months 6
W.K.	182	180	188	188	172	170	166
A.B.	207	204	200	195	190	186	186
S.P.	284	260	242	225	220	204	200
Mean ±S.D.	224 ± 53	215 ±41	210 ±28	203 ±20	194 ±24	187 ±17	200 ± 17

't' test : 0-1 month, 1-2 months, 2-3 months, 3-4 months, 4-5 months, 5-6 months, 0-6 months — $p > 0.05$ (not significant)

Table XXIII shows STG changes in subjects with hypertension, CAD and DM. The monthly mean STG were 224±53, 215±41, 210±28, 203±20, 194±24, 187±17 and 184±17 mg/dl. No two values differed significantly ($p > 0.05$ even for 0-6 months).

TABLE XXIV : Showing serum HDL cholesterol changes in patients of hypertension with diabetes mellitus and CAD.

Name	Values of HDL cholesterol(mg/dl)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
W.K.	32	30	34	34	36	38	38
A.B.	38	40	40	46	48	48	48
S.P.	36	30	30	36	37	37	38
Mean ±SD	35±3	33±6	35±5	39±6	40±7	41±6	41±6
't' test :	0-1 month 1-2 months 2-3 months 3-4 months 4-5 months 5-6 months 0-6 months			p > 0.05 (not significant)			

Table XXIV shows serum HDL changes in patients of hypertension with DM and CAD. The monthly mean HDL values were 35±3, 33±6, 35±5, 39±6, 40±7, 41±6 and 41±6 mg/dl. No two values were different statistically ($p > 0.05$ even for 0-6 month).

Table XXV shows changes in fasting blood sugar in patients with hypertension, DM and CAD. The monthly mean fasting blood sugar levels were 185±82, 119±53, 120±35, 115±35, 113±31 and 109±27 mg/dl. Again no two

values differ significantly (p $\gtrless$ 0.05 even at 0-6 months).

TABLE XXV : Showing blood sugar(fasting) in patients of hypertension with diabetes mellitus and CAD.

Name	Values of blood sugar(fasting) (mg/dl).						
	Month 0	Month 1	Months 2	Months 3	MOnths 4	Months 5	Months 6
W.K.	132	88	100	94	94	94	94
A.B.	280	180	160	155	148	148	140
S.P.	144	88	99	96	96	96	94
Mean ±S.D.	185 ±82	129 ±53	120 ±35	115 ±35	113 ±31	113 ±31	109 ±27

't' test :		
	0-1 month	p $\gtrless$ 0.05
	1-2 months	
	2-3 months	
	3-4 months	
	4-5 months	
	5-6 months	
	0-6 months	

TABLE XXVI : Showing changes in dose of antidiabetes drug in patients of hypertension, CAD and diabetes mellitus.

Name	Dose of antidiabetics (Glibendamide) (mg/day)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
W.K.	7.5	7.5	7.5	5	5	5	5
A.B.	15	15	15	15	15	15	15
S.P.	15	15	15	10	10	10	10
Mean ±S.D.	12.5 ±4.1	12.5 ±4.1	12.5 ±4.1	10±5	10±5	10±5	10±5

't' test :		
	0-1 month	p $\gtrless$ 0.05 (insignificant)
	1-2 months	
	2-3 months	
	3-4 months	
	4-5 months	
	5-6 months	
	0-6 months	

Table XXVI shows changes in the requirement of antidiabetic drug glibendamine in the patients with hypertension, DM and CAD. The mean initial daily requirement was 12.5±4 mg and it remained same for 3 months. Thereafter, the requirement was 10±5 mg/day. However, there was no statistically significant change ($p > 0.05$).

Table XXVII shows the changes in blood pressure in subjects of hypertension with diabetes mellitus and CAD. The monthly mean systolic blood pressure values were 150±10, 148±11, 139±8, 134±5, 133±6, 135±9 and 137±12 mm Hg. The monthly changes in systolic blood pressure were significant for first 3 months ($p < 0.05$), but insignificant later on ($p > 0.05$). The total change in systolic blood pressure from 0 to 6 month was also significant ($p < 0.05$). Similarly, the monthly mean diastolic blood pressure were 104±7, 93±3, 88±2, 91±5, 90±5, 89±8 and 89±9 mm Hg. This time, no two values were statistically different. ($p > 0.05$ even for 0 to 6 months).

TABLE XXVII : Showing changes in systolic and diastolic blood pressure in patients of hypertension withdiabetes mellitus and coronary artery disease.

Name	Values of systolic and diastolic blood pressure (mm Hg)													
	0 month		1 month		2 months		3 months		4 months		5 months		6 months	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D
W.K.	160	110	160	96	148	90	140	96	140	96	146	98	150	100
A.B.	140	96	140	90	136	86	132	88	130	88	130	86	130	84
S.P.	150	106	144	94	134	88	130	88	130	86	130	84	130	84
Mean ±S.D.	150 ±10	104 ± 7	148 ±11	93 ± 3	139 ± 8	88 ± 2	134 ± 5	91 ± 5	133 ±6	90 ± 5	135 ± 9	89 ± 8	137 ±12	89 ± 9

't' test :

Systolic BP

p $<$ 0.05	0 : 1 month
p $<$ 0.05	1 : 2 months
p $<$ 0.05	2 : 3 months
p $>$ 0.05	3 : 4 months
p $>$ 0.05	4 : 5 months
p $>$ 0.05	5 : 6 months
p $<$ 0.05	0 : 6 months

Diastolic BP

p $>$ 0.05

TABLE XXVIII : Showing changes in dose of antihypertensive drug(Atenolol) in patients of hypertension with CAD and DM.

Name	Dose of antihypertensive(Atenolol) (mg/day)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
W.K.	50	50	50	50	50	50	50
A.B.	100	100	100	100	100	100	100
S.P.	100	100	100	100	100	100	100
Mean ±S.D.	83 ±29	83 ±29	83 ±29	83 ±29	83 ±29	83 ±29	83 ±29

0 to 6 months change = 0

Table XXVIII shows change in the daily requirement of antihypertensive agent atenolol in those subjects who were having hypertension, DM and CAD. It is clear from the table that the mean initial requirement was 83±29 mg/day and it remained the same throughout the study.

TABLE XXIX : Showing ECG changes in patients of hypertension with diabetes mellitus and CAD.

Name	S-T segment depression (mm)						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
W.K.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
A.B.	0	0	0	0 0	0	0	0
S.P.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mean ±S.D.	0.3 ±0.3	0.3 ±0.3	0.3 ±0.3	0.3 ±0.3	0.3 ±0.3	0.3 ±0.3	0.3 ±0.3

0 to 6 months change = 0

Table XXIX shows the S-T segment depression in ECGs of patients with hypertension, DM and CAD. It is obvious that the mean ST segment depression was 0.3±0.3 mm initial and it did' not change throughout the study period.

TABLE XXX : Showing change in dose of antianginal drug in patients of hypertension with diabetes mellitus and CAD.

Name	Dose of antianginal (Sorbitrate), mg/day						
	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
W.K.	30	30	30	30	30	30	30
A.B.	30	30	30	30	30	30	30
S.P.	30	30	30	30	30	30	30
Mean±SD	30±0	30±0	30±0	30±0	30±0	30±0	30±0

0 to 6 months change = 0

Table XXX shows changes in the requirement of antianginal drug sorbitrate in patients of hypertension with diabetes mellitus and CAD. Again, it is obvious that the initial requirement was 30±0 mg/day and it remained the same throughout the study period.

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D I S C U S S I O N

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D I S C U S S I O N

Ischemic heart disease has become the most important cause of premature death and disability. The disease may result in sudden death or it may manifest itself as an acute and often fatal attack of myocardial infarction or as angina pectoris. It remains the leading cause of death inspite of all efforts made by scientists in the field of investigations and treatment. The disease has been studied in different parts of the world and the new techniques are coming day by day but still we have to know a lot about them. One of the major risk factor for myocardial infarction is hyperlipidemia (hyperlipoproteinemia) leading to atherosclerosis. Medical scientists are of the opinion that hypolipidemic, antidiabetic and antihypertensive drugs and other measures that can decrease - catecholamine levels are considered to be remedy for myocardial infarction (Haab, 1971).

High blood pressure is an important risk factor for atherosclerotic arterial diseases mainly ischemic heart disease and cerebrovascular disease. The risk increases progressively with increasing blood pressure. In the Framingham study, ischemic heart disease incidence in middle aged men with blood pressure exceeding 160/95 was more than five times, that in normotensive men (blood pressure 140/90 or less). Hypertensive men and women are both affected with the diastolic pressure perhaps being more important.

Diabetes mellitus, a generalised pan-metabolic disorder, is a global disease and is of much concern to the clinicians all over the world, due to the increasing recognition of the wide spread prevalence and manifold complications. The complications of diabetes mellitus which involve almost all the systems of body, are becoming the main havoc for the diabetic population. It is the occurrence of these multisystem long term complications which is responsible for the ranking of the disease as a forth leading cause of death in the world.

Vigorous global research is going on to search the agents to control hyperlipidemia, diabetes mellitus and hypertension. Indian scientists have directed their research towards herbs having hypolipidemic and cardio-protective potential based on few references in age old Ayurvedic texts (Satyavati, 1966). The present study was done on a new combination of similar 3 drugs, namely C.mukul, T. arjuna and I. racemosa. It was conducted in the department of medicine, M.L.B. Medical College, Jhansi to :-

1. Analyse its effect in hypertension, diabetes mellitus and coronary artery disease.
2. Analyse its effect on STC, STG and HDL.

The effects seen by us are as follows :

1. <u>SERUM TOTAL CHOLESTEROL</u>

The effect of the drug in different groups of

patients was studied. In all of the groups, there was a significant fall in serum total cholesterol. Thus our findings support the previous studies done on the same compounds.

Tiwari et al (1990) and Pathak et al (1990) reported a fall in STC by T. arjuna. Similarly, Dwivedi et al (1988) reported hypolipidemic activity of I.racemosa.

Malhotra et al (1973, 1974) observed that fraction A of C. mukul decreases the input/synthesis of cholesterol, whereas Tripathi et al (1975) observed increase in the rate of degradation of cholesterol by activation of thyroid gland as the cause of fall in STC. According to Satyavati (1966), STC was reduced due to its trapping out of intrahepatic circulation.

Dwarkanath and Satyvati (1970) carried out clinical studies on 22 patients and used crude guggulu in a dose of 5-12 g/day for 15-30 days and observed a fall in STC.

Malhotra et al (1971) used fraction A of gum guggulu in a dose of 1 g daily for 6-34 weeks and observed a significant reduction in STC.

Guggulu was tried on 25 patients in a dose of 12-16 g/day for 12 weeks and serum cholesterol was found to be reduced by 22.8% (Upadhyay et al, 1976).

The effect of the drug guggulu was studied on 75 patients in a dose of 6-8 g/day for 12 weeks and a fall in STC by 24.5% was observed by Tripathi et al (1976).

Malhotra et al (1977) conducted a long term study on fraction A of gum guggulu in a dose of 1.5 g/day for 75 weeks and observed a fall in STC as high as 36.8% whereas Kuppurajan et al (1978) could get a fall in STC by only 4.5%.

Gupta et al (1978) gave the same drug to 25 patients in a dose of 12-16 g/day for 12 weeks and got a 35.8% reduction in STC, while Saxena (1980) obtained reduction by 15%. Similar results were seen by Agarwal et al (1986). Upadhyaya and co-workers (1982) achieved 27% fall in STC by 12 weeks.

Katiyal et al (1984) used fraction A of guggulu and observed a significant reduction in STC.

The combination of two drugs, C. mukul and I.racemosa was used for the 1st time by Malhotra et al (1984) and he observed a fall in STC by 17.4%.

Finally, the same drug (combination of all 3 drugs) was used by Gupta et al (1993) in the same dose for 3 months and a fall in STC by 11.2% was observed.

Thus our observations on STC are similar to the previous trials.

SERUM TRIGLYCERIDES (STG)

Tiwari et al (1990) and Pathak et al (1990) reported triglyceride lowering effect of T. arjuna. In a study, clinical efficacy of fraction A of gum guggulu as hypolipidemic agent was evaluated in comparison to ethyl-p-

chlorophonery Psebutyrate and CIBA-13437-SV. Fraction A of gum guggulu was administeredin the dose of 1 gm in two divided doses daily. The duration of treatment varried from 6 to 34 weeks. Statistical analysis revealed that fraction A lowered significantly the serum triglycerides besides lowering other lipid fractions and the lowering of triglyceride was found most encouraging in case of gum guggulu in comparison to all the known drugs (Malhotra et al, 1971). Similarly the other workers have noted a triglyceride lowering effect of C. mukul (Malhotra et al, 1977; Upadhyaya et al, 1976; Gupta et al, 1978; Saxena, 1980; Agarwal et al, 1986; Upadhyaya et al, 1982; Kotiyal et al, 1984; Tripathi et al, 1984).

Whereas all these studies had favourable results on triglyceride, Gupta et al (1993) used the same drug for 3 months but didn't observe any effect on STG.

It was found in present study that the drug was effective in lowering the serum triglyceride only in hyper tensive group and those patients who were having both hypertension and coronary artery disease. The insignificant effect in the rest of the two groups may be due to the fact that the studied population was too small. Also the serum triglycerides shows more day to day variability than STC.

SERUM HDL

Tiwari et al (1990) reported an increase in HDL cholesterol levels by T. arjuna, similarly Pathak et al (1990) also observed an increase in serum HDL cholesterol in rabbits by T. arjuna.

In the multicentric clinical trials on guggulipid in a dose of 500 mg thrice daily for 12 weeks, conducted by Central Drug Research Institute (CDRI), Lucknow, an HDL increase of 13.3%, 30.1%, 6.4% and 20.4%, was reported from Bombay, Jaipur (a & b) and Lucknow respectively. The average increase was 16.07%.

In 1993, Gupta et al conducted clinical trials, on 30 patients with hyperlipidaemia. He gave the combination of C.mukul (500 mg), T.arjuna (500 mg) and I.racemosa (500 mg) in a dose of two capsules twice daily for 3 months. He observed in rise in HDL of 10% after 3 months of therapy and it was statistically significant.

However, we didn't observe any rise in serum HDL cholesterol in any of the four groups of our study. The reason is clear. We didn't choose the patients of hyperlipidemia who could have low initial serum HDL cholesterol.

EFFECT ON BLOOD PRESSURE

Our observations on the effect of the drug in lowering systolic and diastolic blood pressure are variable in different groups of patients. In the first

group (hypertensive subjects), there was a significant reduction in both the systolic and diastolic blood pressures. Also, the requirement of the antihypertensive drug atenolol was reduced in these patients.

In subjects with hypertension and coronary artery disease, we observed reduction in systolic blood pressure only. Whereas there was no change either in the diastolic blood pressure or in the requirement of atenolol.

In patients who were having both hypertension and diabetes mellitus, there was decrease in both diastolic and systolic blood pressures but no effect was seen in the requirement of antihypertensive drug atenolol.

In subjects with all 3 risk factors for atherosclerosis, only systolic blood pressure fell significantly by taking the drug for 6 months.

Dwivedi et al (1988) observed that T. arjuna possesses antihypertensive activity. Pathak et al(1987) also observed similar effects of the drug.

In a trial on the effect of Inula racemosa hook, Dwivedi et al (1989) found that it reduced diastolic blood pressure.

Ambasta (1986) found T. arjuna to be effective in hypertension.

Thus out findings are not dissimilar the previous reports on the component drugs of the combination we have used.

CORONARY ARTERY DISEASE

Though, all the said parameters are risk factors for coronary artery disease,,but it is essential to observe the direct effect of the drug on anginal episodes, electrocardiographic changes and changes in the requirement of antianginal drug sorbitrate.

Dwivedi et al (1987; 1988) reported that T.arjuna enhanced PGE_2 like activity and thus helps preventing myocardial ischemia. It delayed the onset of myocardial ischemia in pre treated animals.

Tripathi et al (1984a) observed antianginal property of I. racemosa.

Guggulu was tried on 25 patients of coronary insufficiency, 12-16 g/day of the drug was administered for 12 weeks. Depression of ST segment and correction in T wave inversion was observed in ECGs of all the patients (Upadhyaya et al, 1976).

Upadhyaya and co-workers (1982) studied the effect of guggulu powder on long series of patients. Guggulu powder in the dose of 8 g/day was administered to 135 patients of ischaemic heart disease for a duration of 12 weeks. Complete improvement in precardial pain was noted in 75% of patients, 14% of patients showed complete improvement in ECG changes of ischaemic heart disease.

A 1 : 1 combination of guggulu and pushkaramoola (I. racemosa) was observed for its clinical efficacy on the patients of ischaemic heart disease. The drug was

dispensed in the dose of 6 g/day for 16 weeks to 50 patients of ischaemic heart disease. The results showed that 10% cases were cured (no precardial pain and ECG abnormalities normalised), 60% patients relieved(improvement only in precardial pain). However, no improvement was observed in remaining 10% of the cases (Tripathi et al, 1984).

Dwivedi (1988) confirmed the efficacy of the drug in reducing intensity and frequency of angina pectoris.

The root powder of I. racemosa was tried in 9 patients of ischaemic heart disease. It showed significant prevention of post exercise ST segment depression in all the patients of IHD and results were found to be comparable to nitroglyceride (Tripathi et al, 1984a). Further, a combination of root powder of I.racemosa and also gum resin of C. mukul (guggulu) in the dose of 6000 mg/day was given to 50 patients of ischaemic heart disease. It completely cured 5 patients, significant improvement in ECG was noted in 40 patients and 5 patients failed to respond to drug (Tripathi et al, 1984b).

In a study on a series of 60 patients the water extract of I.racemosa was given in the dose of 1.5 g/day significant reduction in number of episodes of angina pectoris, significant improvement in ST depression and T.wave inversion in ECGs of patients were important observations (Dwivedi et al, 1989).

However, we did not observe any effect on the ST segment. Nor these was any change in the requirement of

the antianginal drug, sorbitrate.

DIABETES MELLITUS

We observed reduction in the fasting blood sugar level only in those patients who were having hypertension and diabetes mellitus. However, there was no reduction in the requirement of oral hypoglycaemic drug glibendamide.

Dwivedi et al (1988) observed hypoglycemic effect of T. arjuna and I. racemosa in separate studies. Sharma et al (1978), however, failed to find any significant hypoglycaemic effect in rabbits, four hours after administration of alcoholic extract of I. racemosa.

Recently in another study 500 mg powder of T. arjuna was administered in 30 patients of stable angina pectoris. The drug was useful in alleviating the anginal pain. It was also noted to be useful in the cases of IHD associated with rhythm disturbances, pariticularly premature beats. The drug was found to be beneficial in modifying various non-coronary risk factors like obesity, hypertension, diabetes mellitus and circulating catecholamines in these patients.

Thus our findings support the views expressed by previous workers.

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SUMMARY AND CONCLUSION

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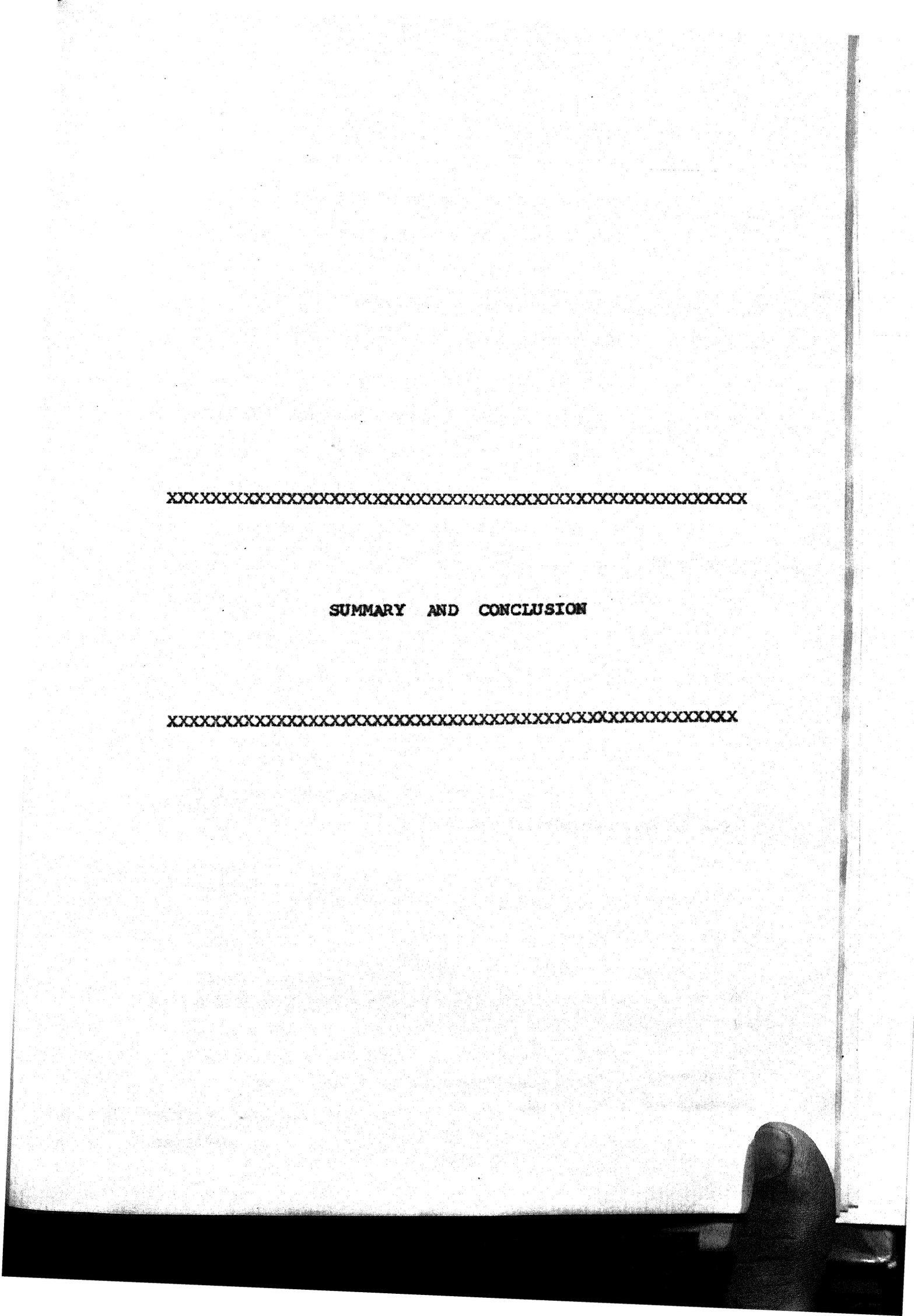

SUMMARY AND CONCLUSION

The present study was carried out on 25 subjects having hypertension, diabetes mellitus and coronary artery disease in the department of Medicine, M.L.B. Medical College, Jhansi. They were given a new combination of age old herbal drugs C.mukul, T.arjuna and I.racemosa in the form of two capsules twice daily for 6 months. Initial and monthly blood samples were taken and changes in ECG, blood pressure and requirement of antihypertensive drug (atenolol), antidiabetic drug (glibendamide) and antianginal drug (isosorbitrate) were recorded. The blood samples were analysed for total cholesterol, triglyceride, HDL cholesterol and blood sugar. The collected data were analysed by student's 't' test and following conclusions were drawn.

1. In all of the groups, there is a significant fall in serum total cholesterol.
2. The drug is effective in lowering the serum triglyceride only in the hypertensive group.
3. There is no effect on serum HDL cholesterol in any group.
4. There is variable effect on hypertension in different groups. As a generalization, the drug lowers systolic as well as diastolic blood pressure.
5. The drug has no antianginal action. Also it has no effect on ECG abnormalities of ischaemic heart disease.
6. The drugs also have hypoglycaemic action.

Thus, the drug has hypolipidaemic, antihypertensive and hypoglycaemic actions and is thus cardioprotective.

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B I B L I O G R A P H Y

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A P P E N D I X

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APPENDIX - I

WORKING PROFORMA

EVALUATION OF CTI(CARDIOPROTECTIVE DRUG) IN SUBJECTS OF CORONARY ARTERY DISEASE, HYPERTENSION AND DIABETES MELLITUS

Case No._____

MRD/OPD No. _____ Dated:

Name : Age/Sex :

Religion : Occupation:

Address : Socio-economic status:

Physical Activity : Sedentary/Active/Very active

Any emotional/mental stress in life :

Diagnosis :

Chief Complaints :

PAST HISTORY

FAMILY HISTORY

TREATMENT HISTORY

CLINICAL ASSESSMENT

I. Subjective :

Parameter	Before treatment	During Treatment
Appetite		
Sleep		
Motions		
Activity		
General		
Feeling		
Libido		
Sex life		

II. Objective.

Parameter	Before Treatment	During Treatment	Parameter	Before Treatment	During Treatment
P.R.			Cyanosis		
R.R.			Clubbing		
B.P.			Oedema		
Temperature			Hydration		
Weight			Lymph nodes		
Icterus			J.V.P.		
Pallor			Organomegaly		

LABORATORY ASSESSMENT

I. Routine Investigations

Investigations	Before treatment	During treatment 1	2	3	4	5	6
Blood sugar(Fasting)							
E.C.G.							

II. Lipid Profile

Investigations	Before treatment	During treatment 1	2	3	4	5	6
Serum total cholesterol							
Triglycerides							
HDL cholesterol							

Impression

APPENDIX - II

M A S T E R C H A R T

General characteristics of the subjects.

Sl. No.	Name	Age/ Sex	Weight (kg)	Height (cms)	Diagnosis
1.	R.C.	43/M	79	170	Hypertension + D.M.
2.	S.R.	55/F	70	152	Hypertension
3.	R.S.G.	60/M	68	168	Hypertension + CAD
4.	M.B.	32/F	48	150	Hypertension
5.	G.R.	72/M	72	166	Hypertension
6.	R.K.	73/M	90	160	Hypertension
7.	R.S.	55/M	86	158	Hypertension + CAD
8.	W.K.	40/F	90	150	Hypertension+DM+CAD
9.	D.	70/F	60	146	Hypertension
10.	R.D.	75/M	68	170	Hypertension + DM
11.	B.D.	43/F	67	153	Hypertension
12.	M.R.	65/M	45	150	Hypertension
13.	U	32/F	48	145	Hypertension
14.	R.N.	69/M	55	150	Hypertension + CAD
15.	A.B.	80/F	87	155	Hypertension+DM+CAD
16.	N.K.	40/F	66	150	Hypertension
17.	B.K.	61/M	69	164	Hypertension
18.	S.P.	65/F	71	148	Hypertension+DM+CAD
19.	P.L.	60/M	68	166	Hypertension + CAD
20.	S.	58/F	61	152	Hypertension + DM
21.	P.	30/F	56	149	Hypertension
22.	P.N.S.	54/M	72	160	Hypertension + DM
23.	S.K.	56/F	76	152	Hypertension
24.	R.K.A.	52/M	77	168	Hypertension + DM
25.	P.D.	42/F	68	142	Hypertension + CAD

APPENDIX - II

MASTER CHART

Name	Serum total cholesterol(mg%) Months							Serum HDL cholesterol(mg%) Months							Serum triglycerides (mg%) Months						
	0	1	2	3	4	5	6	0	1	2	3	4	5	6	0	1	2	3	4	5	6
RC	205	205	200	200	200	190	180	45	45	48	50	50	50	52	177	170	160	155	152	152	150
SR	308	280	260	292	300	285	263	37	35	35	37	39	39	41	223	200	188	188	180	180	176
RSG	308	296	262	246	230	218	210	30	30	30	35	38	40	40	260	190	172	164	162	160	160
MB	192	190	176	170	170	170	178	45	45	46	48	48	48	48	69	64	60	58	58	58	58
GR	269	260	230	220	200	198	198	35	38	40	40	40	42	42	231	202	186	186	178	178	176
RK	182	200	200	190	190	194	194	42	42	42	40	42	42	43	107	120	120	126	120	120	110
RS	269	260	260	230	220	210	206	36	40	44	45	44	45	45	200	200	187	176	176	170	170
WK	220	208	200	192	190	188	182	32	30	34	34	36	38	38	182	180	188	188	172	170	166
D	250	242	230	224	212	206	200	30	36	35	40	40	40	40	161	166	150	146	144	140	136
RD	192	190	198	198	170	170	168	28	35	35	35	36	36	37	155	155	155	150	142	138	138
BD	250	244	232	225	220	216	212	38	38	38	40	40	41	41	130	130	128	128	126	122	120
MR	173	170	170	166	154	154	154	36	38	44	45	46	46	46	84	80	72	70	74	76	76
U	211	210	208	190	182	170	160	50	50	52	50	50	50	50	70	70	66	66	64	64	63
RN	255	250	240	228	222	210	202	40	44	42	48	47	47	46	164	160	156	154	150	150	138
AB	198	196	190	190	184	170	167	38	40	40	46	48	48	48	207	204	200	195	190	186	186
NK	211	200	192	198	198	190	170	30	36	38	35	36	36	37	177	175	175	170	170	166	160
BK	231	230	212	206	208	208	216	34	38	38	36	38	39	39	223	210	202	190	182	180	172
SP	250	242	236	250	236	228	220	36	30	30	36	37	37	38	284	260	242	225	220	204	200
PL	182	180	188	190	178	178	175	30	30	36	38	39	39	40	92	90	90	86	84	84	80
S	260	260	252	235	220	200	189	30	32	38	46	46	45	45	192	180	156	140	132	124	120
P	211	204	200	194	200	186	178	32	38	44	44	42	42	44	160	162	160	138	130	122	120
PNS	173	170	170	170	162	160	152	36	38	44	45	45	43	43	84	80	72	70	70	68	66
SK	308	290	270	256	248	240	235	30	28	36	38	38	40	41	161	170	170	150	150	140	142
RKA	202	200	192	190	190	180	182	38	40	44	46	45	46	46	146	140	130	150	150	152	150
PD	234	210	210	200	200	200	200	32	36	40	44	44	44	43	175	136	140	152	152	150	144

APPENDIX - III

Blood pressure of subjects (mm Hg)

Name	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.C.	170/110	170/100	160/96	150/96	150/90	148/90	148/90
S.R.	148/106	140/100	140/100	140/100	138/96	140/100	144/100
R.S.G.	150/96	146/90	140/90	136/86	136/86	136/84	136/84
M.B.	139/98	160/80	152/80	140/76	140/76	140/74	136/74
G.R.	140/100	140/92	130/80	130/80	132/80	132/80	130/80
R.K.	146/100	150/100	150/100	150/100	146/98	146/98	146/98
R.S.	160/96	166/90	166/98	160/98	156/98	158/100	156/98
W.K.	160/110	160/96	148/90	140/96	140/96	146/98	150/100
D.	180/80	162/76	160/76	136/76	132/74	132/74	130/70
R.D.	140/98	138/98	140/98	136/78	136/76	136/76	136/76
B.D.	160/120	158/110	140/92	140/90	136/94	136/94	138/96
M.R.	186/120	172/110	160/100	148/94	140/90	140/90	136/88
U.	140/98	140/86	134/86	130/86	130/86	130/84	130/84
R.N.	166/80	158/82	160/80	150/80	144/80	142/80	140/80
A.B.	140/96	140/90	136/86	132/88	130/88	130/86	130/86
N.K.	180/100	176/96	170/96	152/88	150/88	146/84	146/84
B.K.	212/136	180/136	160/100	146/98	146/98	150/100	150/100
S.P.	150/106	144/94	134/88	130/88	130/86	130/84	130/84
P.L.	146/96	146/96	140/90	110/90	106/90	108/76	108/76
S.	190/124	174/106	144/100	138/96	138/96	132/94	130/90
P.	170/120	154/100	150/90	144/86	144/86	140/82	140/82
P.N.S.	180/110	170/98	146/98	142/98	142/98	140/98	140/98
S.K.	168/100	160/100	156/98	156/98	152/98	150/96	150/96
R.K.A.	160/100	160/98	162/94	160/98	156/96	150/96	150/94
P.D.	136/98	136/98	136/98	130/98	132/98	132/98	136/98

APPENDIX - IV

Daily requirement of antihypertensive drug(Atenolol)(mg).

Name	Month 0	Month 1	Months 2	Months 3	Months 4	Months 5	Months 6
R.C.	100	100	100	100	75	75	50
S.R.	50	50	50	50	50	50	50
R.S.G.	50	50	50	50	50	50	50
M.B.	100	100	100	100	75	75	50
G.R.	100	100	100	100	75	75	75
R.K.	50	50	50	50	50	50	50
R.S.	100	100	100	100	100	100	100
W.K.	50	50	50	50	50	50	50
D.	100	100	100	100	100	100	100
R.D.	50	50	50	50	50	50	50
B.D.	50	50	50	50	25	25	25
M.R.	50	50	50	50	50	50	50
U.	100	100	100	100	50	50	50
R.N.	50	50	50	50	50	50	50
A.B.	100	100	100	100	100	100	100
N.K.	100	100	100	100	75	75	75
B.K.	50	50	50	50	50	50	50
S.P.	100	100	100	100	100	100	100
P.L.	100	100	100	100	75	75	75
S.	50	50	50	50	50	50	50
P.	100	100	100	100	100	100	100
P.N.S.	100	100	100	100	100	75	50
S.K.	50	50	50	50	50	50	50
R.K.A.	50	50	50	50	50	50	50
P.D.	50	50	50	50	50	50	50